REMARKS

Reconsideration of the rejections set forth in the Office action mailed February 7, 2008 is respectfully requested.

I. Amendments

Claim 19 has been amended to recite that the microbubbles are encapsulated with a filmogenic fluid, the fluid being an aqueous solution or suspension of human serum albumin and, optionally, a polysaccharide. Support is found in the specification at, for example, page 3, lines 14-15 and 25-26 and at page 5, line 28 to page 6, line 2. No new matter is added by any of the amendments.

II. Rejections under 35 U.S.C. §103

Claims 19-24 were rejected under 35 U.S.C. §103(a) as being unpatentable over Porter *et al.* (U.S. Patent No. 6,245,747) in view of Unger *et al.* (U.S. Patent No. 5,542,935). The rejections are respectfully traversed in light of the following remarks.

A. The Claims

Independent claim 19 is directed to a method for delivering a therapeutic agent to a tumor site in a subject, the method comprising:

administering parenterally to a subject a composition comprising perfluorobutane-filled microbubbles containing an antiproliferative chemotherapeutic agent, wherein the microbubbles are encapsulated with a filmogenic fluid, the filmogenic fluid being an aqueous solution or suspension of human serum albumin and, optionally, a polysaccharide; and

allowing the agent to be released at the tumor site without the use of external stimulation.

In a preferred embodiment, the filmogenic fluid an aqueous solution or suspension of human serum albumin and dextrose.

B. The Cited Art

Porter *et al.* describes methods of delivering drugs to target sites by conjugating the drugs to microbubbles in a fluid suspension. After administration of this composition, the microbubbles are exposed to ultrasound, typically at the target site, to cause the microbubbles to cavitate and release the drug. See, for example, column 3, lines 8-12; column 4, lines 20-22; column 7, lines

35-40; column 8, lines 5-11; column 21, lines 26-41; and column 22, line 66 to column 23, line 1.

Unger *et al.* describes the use of "gaseous precursor-filled liposomes" (abstract) containing a therapeutic compound for delivery of the compound. Lipids, such as fatty acids or phospholipids, are the preferred materials for forming the liposomes; see, for example, columns 19-22 of the patent. As discussed further below, the patent does not teach the use of albumin- or protein-coated microspheres, as alleged by the Examiner.

The Unger patent teaches "the use of sonic energy, microwave energy, magnetic energy, or hyperthermia, which is directed to the target area and causes the microspheres to rupture and release the therapeutic compound" (column 4, lines 33-37). This use of ultrasound to release the compound is referred to frequently throughout the patent; see e.g. column 4, lines 50-51; column 5, lines 5-11; column 7, lines 22-25 and 38-41; column 19, lines 17-19; column 28, lines 58-60; column 32, lines 14-15, 43-50, and 57-59; column 34, lines 1-8; column 35, lines 29-33; column 37, lines 43-46, etc.

The Examiner states in the Office Action (page 3) that the use of the external energy source in Porter "is not a requirement for all delivery methods as shown in the '935 [Unger] patent". However, as shown above, the Unger patent also stresses the use of ultrasound (or other energy source) to release the drug from the microspheres. Applicants can find two descriptions in Unger of instances where ultrasound may not be required; however, neither is relevant to protein-encapsulated, perfluorobutane-containing microbubbles as employed by the applicants. The first instance is described at column 33, lines 38-62 of Unger (emphasis added):

> The preferred method of performing site directed drug delivery with the gaseous precursor microspheres is to apply energy to the target tissues and in doing so, release the therapeutics from the microspheres. The most preferred energy source is ultrasound. In certain instances, however, the gaseous precursor microspheres can be extremely effective on their own in terms of locally deliverying drugs. It is believed that gaseous precursors *which undergo a liquid to gaseous phase transition at close to body temperature* are particularly effective at accumulating in ischemic and diseased tissues.... Ultrasound or other energy may be optionally applied to the ischemic tissue to facillitate [sic] drug delivery.

However, the description of "gaseous precursors which undergo a liquid to gaseous phase transition at close to body temperature" would not apply to perfluorobutane, which has a boiling point of about 4°C (as shown in Table 1 of Unger *et al.*).

The second instance is described at column 34, lines 33-40 (emphasis added):

> In applications such as the targeting of the lungs, *which are lined with lipids*, the therapeutic may be released upon aggregation of a gaseous precursor-filled *lipid* microsphere *with the lipids lining the targeted tissue*. Additionally, the gaseous precursor-filled *lipid* microspheres may burst after administration without the use of ultrasound. Thus, ultrasound need not be applied to release the therapeutic *in the above type of administration.*

This situation would not apply to the microbubbles of the current claims, or to those described in Porter, since they are not "lipid microspheres".

Further to this point, the Examiner continues to assert (point 6 in the Office Action) that Unger teaches "protein coated" microbubbles which are "coated with human serum albumin". This is overall a misrepresentation of the teachings of the patent, which repeatedly describes "lipid microspheres" and "liposomes". See, for example, the Abstract; column 4, lines 55 and 61; column 7, lines 46-47; column 9, line 17; the description of preferred lipid materials at columns 19-22; the description of the preparation of the lipid/liposomal compositions at columns 39-52; and all of the working Examples in the patent.

Applicants note that the Abstract of the Unger patent nowhere mentions "protein coated" microbubbles as alleged by the Examiner (item 6 of the Office Action). In fact, the only reference to albumin coating in Unger actually teaches away from using albumin as a coating. Following a discussion of the use of "emulsifying or stabilizing agents" (column 22, last paragraph), the patent states that "flexible stabilizing materials" are preferred (column 23, lines 1-2), and that "microspheres stabilized by albumin and other proteins *are less effective* as these stabilizing coating are *more brittle* and are easily broken during pressure changes" (column 23, lines 2-5; emphasis added). One skilled in the art would clearly see these statements as teaching

reasons not to use "albumin and other proteins" in this role. The subsequent paragraphs (column 23, lines 10-55) describe various stabilizing and emulsifying agents, none of which are proteins.

Thus, contrary to the Examiner's statements, Unger *et al.* describes the use of lipid microspheres, a completely different composition from the albumin encapsulated microbubbles of the instant claims.

In view of the foregoing, there is no indication in the teachings of Porter and Unger, taken in combination, that "perfluorobutane-filled microbubbles containing an antiproliferative chemotherapeutic agent, wherein the microbubbles are encapsulated with a filmogenic fluid, the fluid being an aqueous solution or suspension of human serum albumin and, optionally, a polysaccharide", as recited in the instant claims, would be effective to deliver a therapeutic agent to a tumor site without "the use of external stimulation", which is routinely employed in these two references, and consistently employed in Porter.

In view of the foregoing, the applicant respectfully requests the Examiner to withdraw the rejections under 35 U.S.C. §103(a).

III. Conclusion

In view of the foregoing, the applicant submits that the claims now pending are now in condition for allowance. A Notice of Allowance is, therefore, respectfully requested.

Respectfully submitted,

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